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RESEARCH**

APPLICATION NUMBER: NDA 21-335

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-335

Submission Date: February 27, 2001
April 10, 2001
April 12, 2001

Drug Name: GLEEVEC™ (imatinib, CGP 57148B, STI 571)

Formulation & Strength: Oral Hard Gelatin Capsule, 50 and 100 mg

Applicant: Novartis Pharmaceutical Corp.
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East Hanover, NJ 07936

Reviewer: John Duan, Ph.D.

Pharmacometrics Reviewer: Jogarao Gobburu

Type of Submission: New Drug Application

This is a review of the Clinical Pharmacology and Biopharmaceutics (CPB) studies submitted in NDA 21-335 in support of GLEEVEC™ indicated for the treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy.

I. OVERALL SUMMARY

The applicant has submitted 26 studies in Section 6 (Human Pharmacokinetics and Bioavailability) of this NDA to seek an approval for GLEEVEC indicated for the treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. The recommended dose is 400 mg/day for patients in chronic phase CML and 600 mg/day for patients in accelerated phase or blast crisis and the doses may be increased to 600 mg and 800 mg, respectively, based on tolerance and disease states.

GLEEVEC™ (imatinib mesylate) is a protein-tyrosine kinase inhibitor, which selectively inhibits proliferation and induces apoptosis in Bcr-Abl positive cell lines as well as fresh leukemic cells from Philadelphia chromosome positive chronic myeloid leukemia (CML).

Nonlinear mixed effects pharmacokinetic modeling suggested that body weight and age are the important covariates governing the exposure of imatinib. The WBC counts decrease over time in a concentration dependent manner. No exposure (dose or concentration) – desired effect relationships could be derived for the pharmacodynamic variables – survival and time to (hematologic/cytogenetic) response. A imatinib steady – state concentration and probability of edema relationship was established. Older CML patients are identified to be the sub-population that is most prone to grade 3 or higher edema..

After oral administration, imatinib was absorbed with the C_{max} between 2 and 4 hours. Although Caco-2 cell monolayer transport studies conducted at low drug concentrations showed the drug to be a low permeability drug, the absolute bioavailability of the drug was 98%. Therefore, imatinib is classified as a high permeable drug. At clinically relevant concentrations of imatinib, binding of the parent drug to plasma proteins was approximately 95%, mostly to albumin and α_1 -acid glycoprotein. However, the protein binding of the major active metabolite CGP74588 was not studied. Following oral administration, the elimination half life of the parent drug and the major metabolite, CGP74588 were approximately 18 and 40 hours, respectively. Imatinib AUC was dose proportional at the recommended dose range. Approximately 81% of the dose was eliminated within 7 days, 68% in feces and 13% in urine. The main circulating active metabolite in humans was the N-demethylated piperazine derivative CGP74588 that showed similar in vitro potency as the parent drug. The plasma AUC of this metabolite was 16% of the AUC for imatinib. CYP3A4 was the major enzyme responsible for the metabolism of imatinib. Imatinib exposure increased significantly when GLEEVEC was co-administered with a single 400 mg dose of ketoconazole. A preliminary report showed that imatinib increased the mean C_{max} and AUC of simvastatin (CYP3A4 substrate). Both STI571 and CGP74588 appear to be potent inhibitors of CYP2D6. Therefore, there is a potential for drug interactions between STI571 and CYP2D6 related drugs. There are no pharmacokinetic data in pediatric patients although a study is ongoing. No clinical studies were conducted with GLEEVEC in patients with impaired renal or hepatic functions. However, caution should be exercised when Gleevec is administered to patients with hepatic function impairment. The effects of food on the bioavailability of STI 571 have been evaluated in patients at steady state. Adequate dissolution data were provided.

From Clinical Pharmacology and Biopharmaceutics perspective, the NDA is acceptable. However, reports of ongoing studies and final report of study [] should be submitted for review and labeling update. In addition, a drug interaction study between imatinib and CYP2D6 related drugs is recommended as a Phase IV commitment. Since hepatic elimination is the major elimination pathway for Gleevec and no dose recommendation can be made for patients with liver impairment, a clinical study to evaluate the pharmacokinetics of imatinib in liver impaired patients as a Phase IV commitment is recommended. Further, although the exposure to the major metabolite CGP74588 is 16% of the parent drug, the definite contribution of this metabolite to the overall activity of Gleevec can not be concluded in absence of the plasma protein binding information of the metabolite. Therefore, the protein binding of this active metabolite should be assessed as a Phase IV commitment.

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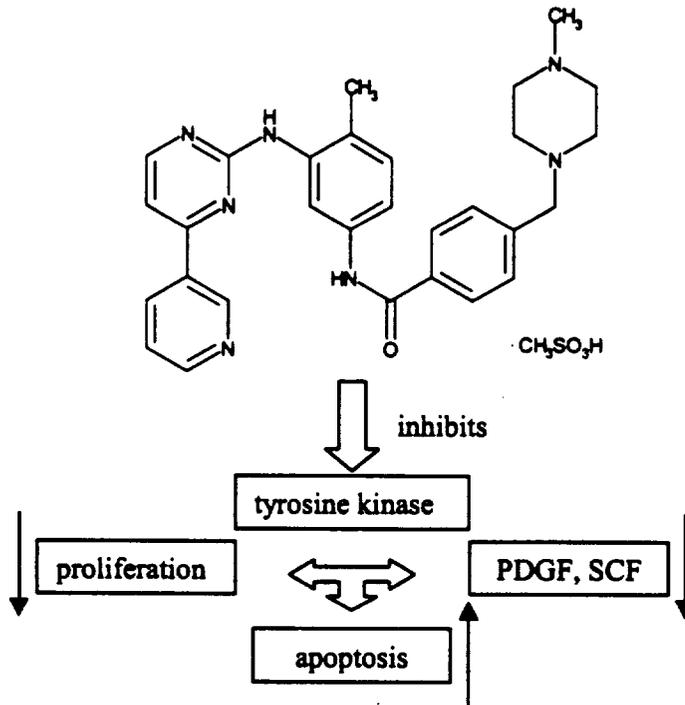
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III. BACKGROUND

General

GLEEVEC™ (imatinib mesylate) is a protein-tyrosine kinase inhibitor, which potently inhibits the Bcr-Abl tyrosine kinase.

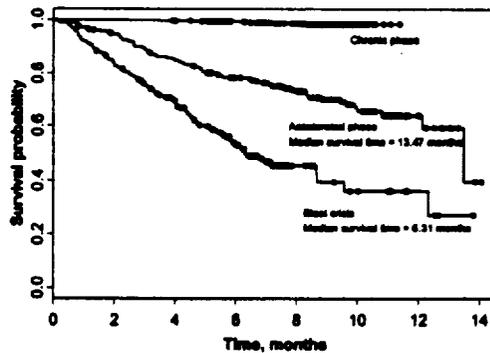


The compound selectively inhibits proliferation and induces apoptosis in Bcr-Abl positive cell lines as well as fresh leukemic cells from Philadelphia chromosome positive chronic myeloid leukemia (CML) and acute lymphoid leukemia (ALL) patients. In addition, imatinib is a potent inhibitor of the receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor (SCF), c-Kit, and inhibits PDGF- and SCF-mediated cellular events.

The applicant has submitted the following studies in Section 6 (Human Pharmacokinetics and Bioavailability) of this NDA to seek an approval for GLEEVEC indicated for the treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy.

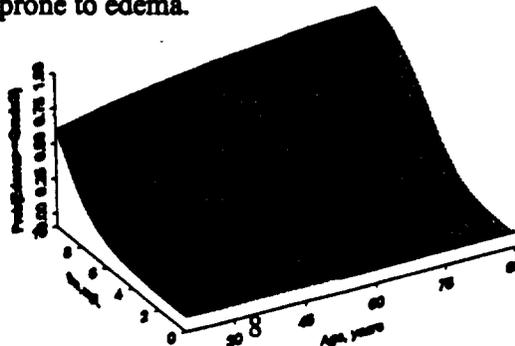
Studies submitted	No. of studies	Number of Subjects		Dose range
		Patients	Healthy volunteers	
Dose finding study	1	591	33	25-1000 mg
Mass balance study	1			
Bioavailability study	1			
Food effect study	1			
Drug interaction studies	2			
PK/PD study	1			
Population pharmacokinetic study	1			
in vitro protein binding studies	5			
In vitro metabolism studies	9			
Dissolution studies	4			
Literature references	7			

The survival of the patients could not be correlated with the concentration/dose. The time to (hematologic/cytogenetic) response, also, could not be correlated with the concentration/dose. The survival probability curves of the CML patients in the 3 different disease states are shown below:

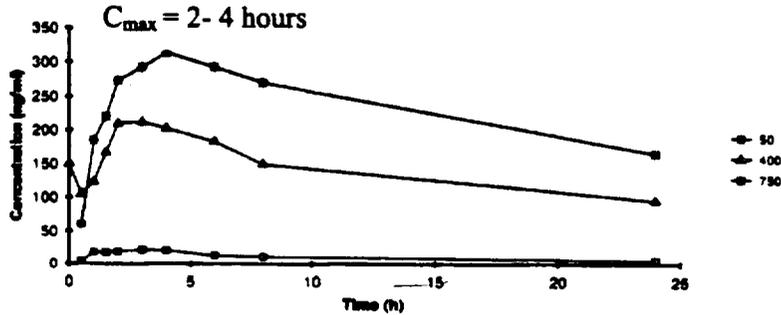


The median survival time for the patients in accelerated and blast crisis were estimated to be 13.47 and 6.31 months, respectively. The fact that most of the patients in blast crisis received 600 mg (and not lower doses) complicates the interpretation. Further, the dose and/or the concentration range is quite narrow and given that the doses are chosen to produce maximum peripheral-WBC count suppression, limits the probability of establishing the relationship in the first place.

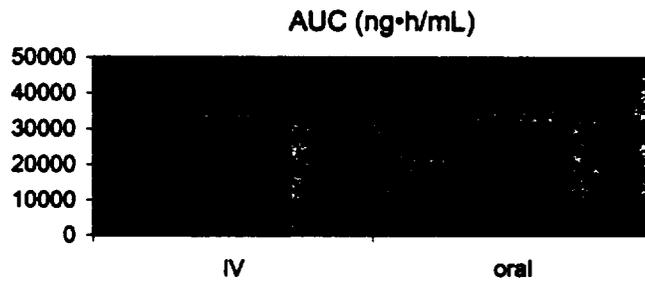
A clear concentration - probability of developing edema relationship was found. The figure below shows the probability of having a grade 3 edema in blast crisis patients. Older patients (age ≥ 65 years) are most prone to edema.



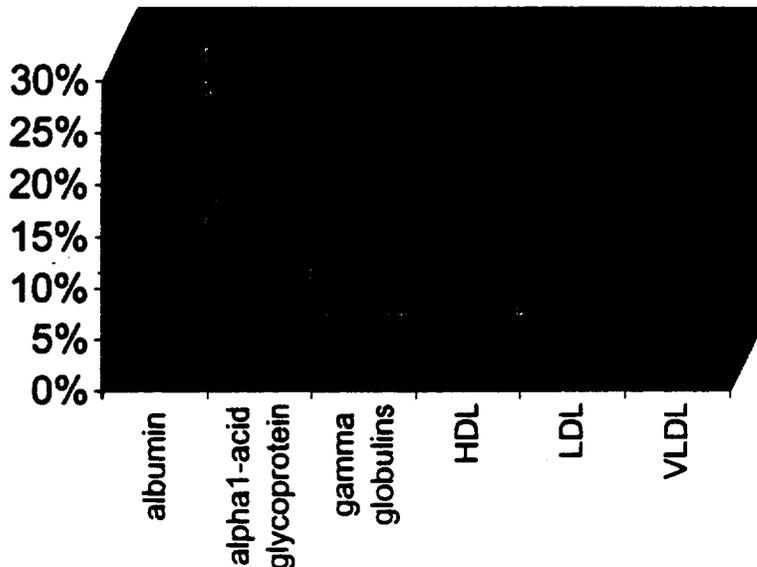
Imatinib was absorbed with the C_{max} being 2-4 hours as shown in the figure below (a typical STI571 concentration vs. time profile).



Mean absolute bioavailability for the capsule formulation is 98%. The coefficient of variation for plasma imatinib AUC is in the range of 40-60% after an oral dose. Following is a comparison of AUC between IV and oral dosing.



At clinically relevant concentrations of imatinib, binding to plasma proteins is approximately 95% on the basis of *in vitro* experiments, mostly to albumin and α_1 -acid glycoprotein, with little binding to lipoprotein as shown in the following figure.

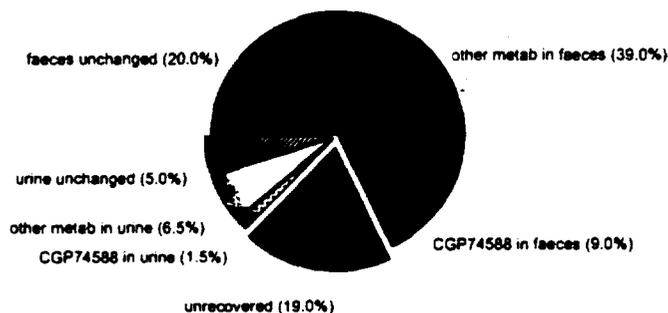


As shown in the table below, *in vitro* studies showed concentration dependent human plasma protein binding.

Concentration in plasma	% bound	Study
µg/mL	95%	DMPK(F) 1998/035
µg/mL	93%	DMPK(F) R99-010
µg/mL	91%	BPK(CH)1995/116
µg/mL	86%	DMPK(F) 1998/035

The main circulating metabolite in humans is the N-demethylated piperazine derivative CGP74588 which shows similar *in vitro* potency as the parent. The plasma AUC for this metabolite was found to be 16% of the AUC for imatinib.

Based on the recovery of compound(s) after an oral ¹⁴C-labelled dose of imatinib, approximately 81% of the dose was eliminated within 7 days in feces (68% of dose) and urine (13% of dose). Unchanged imatinib accounted for 25% of the dose (5% urine, 20% feces), the remainder being metabolites.



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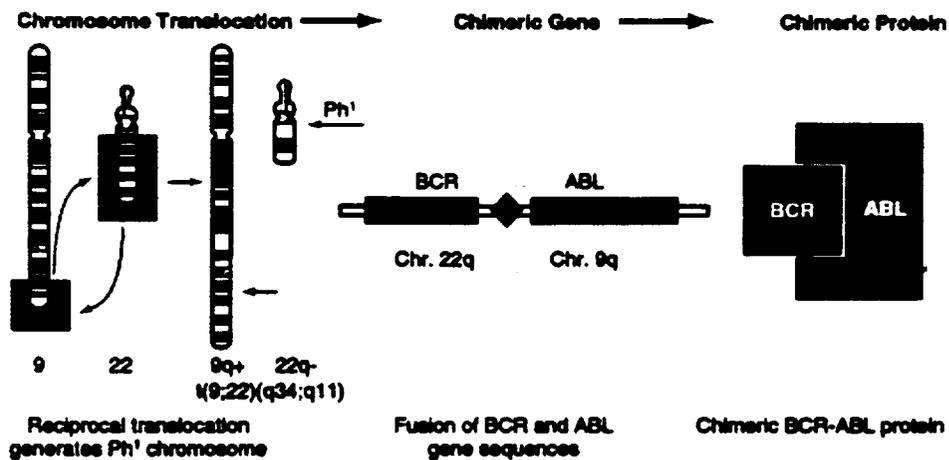
IV. QUESTION BASED REVIEW

This review is completed by using the Question Based Review approach.

1. What is CML? How does STI571 work?

The diagnosis of CML is established by identifying cytogenetically or molecularly a clonal expansion of a hematopoietic stem cell possessing a reciprocal translocation between chromosomes 9 and 22. This translocation results in the head-to-tail fusion of the breakpoint cluster region (Bcr) gene on chromosome 22 at band q11 with the Abl (named after the abelson murine leukemia virus) gene located on chromosome 9 at band q34 as shown in the following figure. The fusion of these DNA sequences allows the generation of an entirely novel fusion protein with modified function. The consequence of expression of the *Bcr-Abl* gene product is the activation of signal transduction pathways, leading to cell growth independent of normal external growth factor signals.

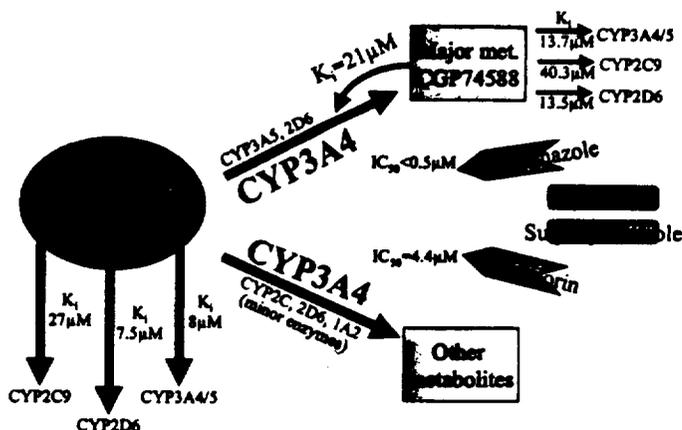
The disease is characterized by the inevitable transition from a chronic phase (median survival: 60-89 months) to an accelerated phase (median survival: <18 months) and on to blast crisis (median survival: 3-6 months).



Imatinib potently inhibits the Bcr-Abl tyrosine kinase. It inhibits proliferation and induces apoptosis in Bcr-Abl positive cell lines as well as fresh leukemic cells from Philadelphia chromosome positive chronic myeloid leukemia (CML) patients. In addition, imatinib is a potent inhibitor of the receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor (SCF), c-Kit, and inhibits PDGF- and SCF-mediated cellular events.

2. How is imatinib metabolized?

Based on the in vitro studies, the metabolism of STI571 is shown in the following figure.



N-desmethyl STI571 (CGP74588) is the major metabolite formed predominantly via CYP3A4. CYP3A5 and CYP2D6 may play a minor role in the formation of the metabolite. CYP3A4 is the major enzyme responsible for the biotransformation of STI571 in human liver microsomes and in cDNA recombinant microsomes expressing specific CYP enzymes. CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 played a minor role in the biotransformation of STI571.

In pooled human live microsomes, 65% of the biotransformation was inhibited by ketoconazole at 1 to 2 $\mu\text{mole/L}$ concentrations. Cyclosporin A also inhibited the formation of the metabolites with an IC_{50} value of 4.4 $\mu\text{mole/L}$ at STI571 concentration of 25 $\mu\text{mole/L}$. Following is a table showing IC_{50} values of various drugs in human liver microsomes.

Drug Names	IC_{50} ($\mu\text{mole/L}$)
Ketoconazole	< 0.5
Cyclosporin A	4.4
Erythromycin	50
Doxorubicin	63
Paclitaxel	70
Ethinylestradiol	63
Terfenadine	54
Astemizole	86
Tamoxifen	200
Carbamazepine	> 200
Warfarin	> 200
Vincristine	> 200
Prednisone	> 200
Cimetidine	> 200

STI571 concentration: 25 $\mu\text{mole/L}$.

Quinidine and Sulfaphenazole, inhibitors of CYP2D6 and CYP2C9, respectively, at 4 $\mu\text{mole/L}$ concentration didn't inhibit biotransformation of STI571.

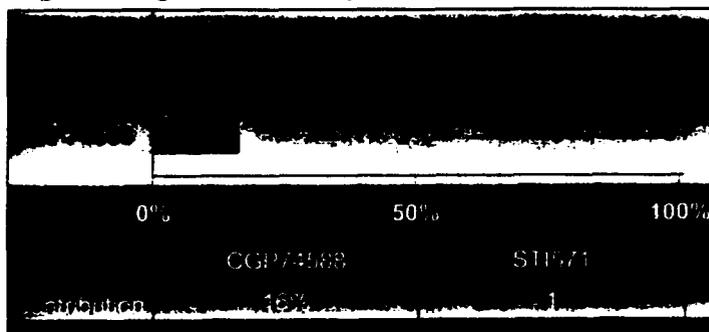
Human liver microsome studies demonstrated that STI571 was a potent competitive inhibitor of CYP2C9, CYP2D6 and CYP3A4/5 with K_i values of 27, 7.5, and 8 $\mu\text{mole/L}$, respectively. STI571 appears to be a competitive inhibitor of CYP1A2, CYP2A6, and CYP2C19 with estimated IC_{50} values of 410, 230, and 120 $\mu\text{mole/L}$, respectively. STI571 didn't inhibit CYP2B6, CYP2E1, and CYP4A9/11. In a pool of liver cytosol prepared from 10 individual donors, STI at 50 $\mu\text{mole/L}$ concentration didn't inhibit metabolism of 5-FU (5 μM .) STI571 is possibly not an inhibitor of cytosolic dihydropyrimidine dehydrogenase, enzyme involved in the catabolism of 5-FU. In pooled human liver microsome, erythromycin and fluconazole inhibited the metabolism of STI571 with IC_{50} values of 50 and 118 $\mu\text{mole/L}$. Acetaminophen, acyclovir, allopurinol, amphotericin, cytarabine, hydroxyurea, norfloxacin, and penicillin V did not inhibit metabolism of STI571 in human liver microsome.

CGP74588 inhibited its own formation with a K_i value of 21 μM . The overall oxidative metabolism of STI571 was inhibited by CGP74588 with a K_i value of 59 μM . The K_M and V_{Max} values of CGP74588 formation from STI571 are 7.8 μM and 139 pmol CGP74588/min/mg. There is a low potential for inhibition of Paclitaxel metabolism by STI571.

In human liver microsome, CGP74588 inhibited CYP 3A4/5 (testosterone 6 β -hydroxylation), CYP2C9 (S-warfarin 7-hydroxylation), and CYP2D6 (bufuralol 1'-hydroxylation) with K_i values of 13.7, 40.3, and 13.5 μM , respectively.

3. What is the role of metabolite?

The major metabolite of STI 571, N-demethylated piperazine derivative, CGP74588 showed similar *in vitro* potency as the parent. A comparison of its mean AUC vs. STI571 AUC following both once daily dosing of 25 mg and twice daily dosing of 1000 mg is shown in the figure below.

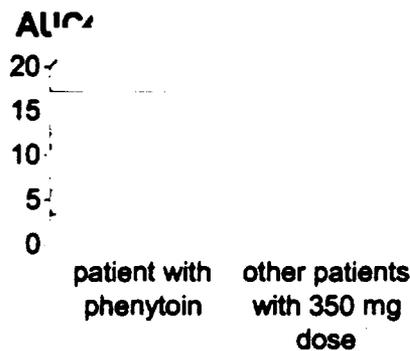


The contribution of this major metabolite in the overall pharmacologic or toxic effect of Gleevec could not be assessed. Although the AUC of the major metabolite was 16% of the parent drug, low plasma protein binding of this metabolite could potentially play a role in the overall pharmacologic or toxic effect of Gleevec. Therefore, the applicant should assess the plasma protein binding of the N-demethylated piperazine derivative of STI571.

4. Is there any clinical relevance of the metabolism of the drug? Does metabolism of imatinib play a role in its overall activity?

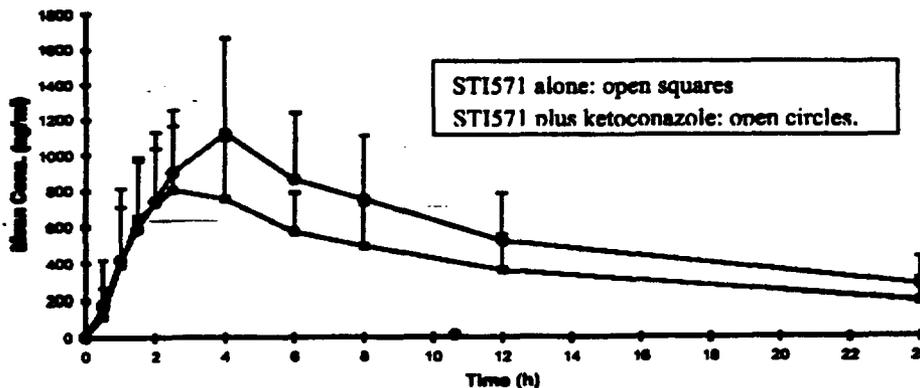
Yes. Metabolism (CYP3A4) plays a vital role in the overall safety and efficacy of the drug.

There are at least three evidences. A drug-interaction was observed involving the induction of metabolism of STI571. A patient treated at a dose of 350 mg daily with concomitant phenytoin therapy failed to respond hematologically and was found to have low plasma levels of STI571 as shown in the following figure.

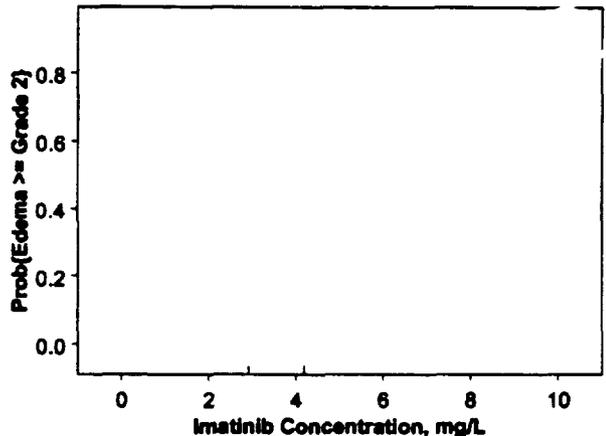


The patient promptly responded when phenytoin was stopped; though simultaneous dose escalation of STI571 to 500 mg was also performed. This is most likely due to the induction of CYP3A4 by phenytoin.

In a drug interaction study, following ketoconazole coadministration, the mean STI571 C_{max} , AUC_{0-24} and $AUC_{0-\infty}$ increased significantly by 26% ($p < 0.005$), 40% ($p < 0.0005$) and 40% ($p < 0.0005$), respectively. Clearance of STI571 in presence of ketoconazole was reduced by 28.6% ($p < 0.0005$). For the metabolite, the mean C_{max} and AUC_{0-24} of CGP74588 decreased significantly by 22.6% ($p < 0.005$) and 13% ($p < 0.05$) after ketoconazole treatment. However, the $AUC_{0-\infty}$ only decreased by 5% and this decrease was not statistically significant ($p = 0.28$). The Figure below shows the mean plasma concentrations of STI571 following oral administration of STI571 alone and when combined with ketoconazole. Since the study was conducted in normal volunteers, the clinical consequence of this interaction is unknown. However, STI571 dose should be reduced when coadministered with CYP3A4 inhibitors.



Using the concentration–edema model developed, the extent of interaction with ketoconazole can be quantitated. The probability of this adverse event is dependent on the age group. For younger blast crisis patients, co-administration of ketoconazole does not increase the probability of edema (Grade 2 or higher), however, for older patients the probability of having edema increases from 13 to 23%, for an average increase in exposure by 40%.

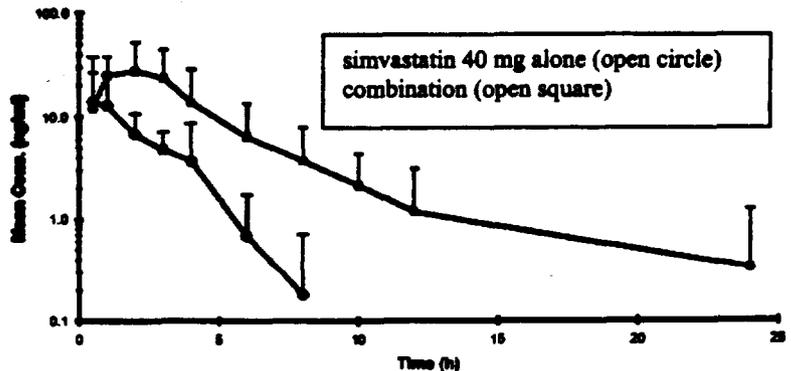


Another drug interaction study in CML patients showed that coadministration of STI571 increased the C_{max} of simvastatin about 2-fold and $AUC_{0-\infty}$ about 3.5-fold compared to those of simvastatin alone. Also the half-life of simvastatin was prolonged from 1.4 to 3.2 h as shown in the following table.

	Simvastatin	Simvastatin plus STI571
t_{max} (h) *	1.6 (0.5 - 4.0)	1.7 (1.0 - 3.0)
C_{max} (ng/mL)	19.9 ± 21.0	37.9 ± 21.1
$t_{1/2}$ (h)	1.4 ± 0.9	3.2 ± 2.3
$AUC_{0-\infty}$ (ng·h/mL)	32.0 ± 25.4	121.9 ± 96.1
AUC_{0-4} (ng·h/mL)	35.8 ± 26.3	133.1 ± 103.2
Vz/F (L)	2902 ± 2129	1657 ± 870
CL/F (L/h)	1567.3 ± 911.6	434.6 ± 216.5

The figure below shows the mean plasma concentrations of simvastatin after oral administration of simvastatin 40 mg alone and combined with STI571 400 mg once daily for 7 days.

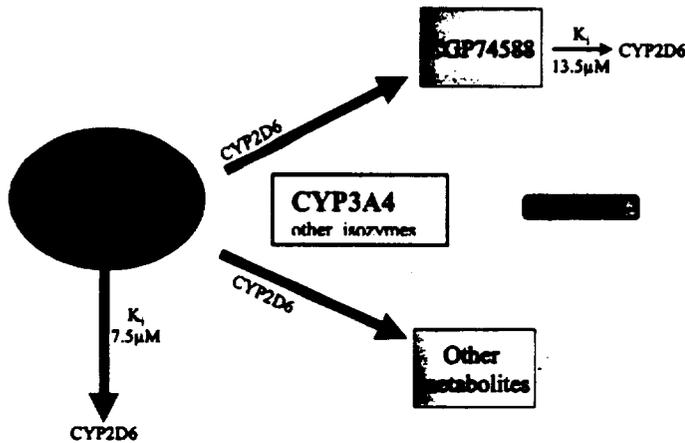
Since the applicant only submitted a preliminary report of the study with 9 patients (total number of patients enrolled is 20), the clinical consequence of this study is unknown.



In summary, CYP3A4 mediated metabolism is involved in the total activity of imatinib. Drugs that are substrates, inhibitors, or inducers of CYP3A4 may have potential interactions with imatinib affecting either the safety or efficacy of the drug.

5. What is the role of CYP2D6?

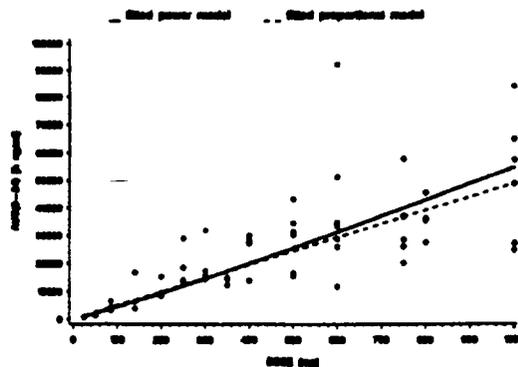
CYP2D6 played a minor role in the biotransformation of STI571 to form CGP74588, the major metabolite and other metabolites as shown in the following figure. Quinidine, a potent inhibitor



of CYP2D6, at $4\mu\text{M}$ concentration did not affect the biotransformation of STI571, indicating an insignificant role of CYP2D6 in the metabolism of STI571. However, both STI571 and CGP74588 appear to be potent inhibitors of CYP2D6 with K_i values of 7.5 and $13.5\mu\text{M}$, respectively. The impact of CYP2D6 inhibition by STI 571 on the pharmacokinetics of drugs, which are substrates of CYP2D6, is unknown. Currently, no dosage recommendation can be made for patients who will be taking drugs that are substrates of CYP 2D6. Therefore, the applicant should assess potential drug interaction between imatinib and a substrate of CYP2D6.

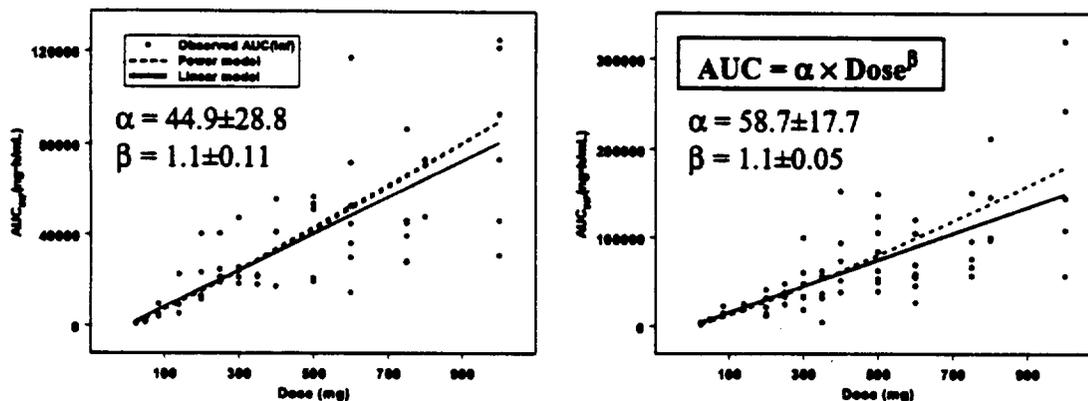
6. Is the dose proportionality established?

The recommended dose of Gleevec is from 400 mg to 800 mg daily depending upon the tolerability and the disease state. The applicant provided the following Figure to show the linear relationship between AUC_{0-24} and administered dose on day 1 after a single oral dose of STI571.



Similar relationship between the AUC_{0-24} and dose was obtained for the steady state.

In order to confirm if the relationship exists between the $AUC_{0-\infty}$ and dose, the reviewer checked the dose proportionality by fitting the $AUC_{0-\infty}$ data to a power model with proportion error. Similar results were obtained as shown in the following figure. The left panel shows the results on Day 1 and the right at steady state.



Therefore, the drug appears to be dose proportional in the dose range 25–1000 mg. However, the variability in AUC is high.

7. Is there any accumulation when multiple doses are given?

The following table is a comparison of PK parameters (mean \pm SD) for STI571 on day 1 and at steady state.

Dose (mg)	$t_{1/2, \text{day 1}}$ (h)	$t_{1/2, \text{SS}}$ (h)	$AUC_{\text{SS}}/AUC_{\text{D1}}^*$	$C_{\text{max,SS}}/C_{\text{max,D1}}^*$
25	12.66 \pm 1.79	14.50 \pm 0.67	2.41 \pm 0.73	2.43 \pm 0.8
400	14.79 \pm 5.79	19.31 \pm 4.37	1.51 \pm 0.57	1.14 \pm 0.36
600	10.85 \pm 2.03	15.60 \pm 5.01	2.22 \pm 2.79	1.72 \pm 1.97
800	16.69 \pm 3.72	19.63 \pm 2.55	1.89 \pm 0.76	1.68 \pm 0.70
1000	11.13 \pm 3.39	16.98 \pm 5.44	1.76 \pm 0.70	1.52 \pm 0.98

* AUC_{SS} , $C_{\text{max,ss}}$ and AUC_{D1} , $C_{\text{max,D1}}$ are values at steady state and on day 1, respectively. Both ratios can be used to estimate the accumulation index.

There is no significant accumulation of STI571 at steady state at doses between 25 and 1000 mg.

8. Is there any food effect on imatinib?

The food effect study was performed while patients were at steady state. As the tables show, when the drug was taken after consuming a fat-rich meal, t_{max} was later, AUC and C_{max} were lower and $t_{1/2}$ was longer than when the drug was taken in the fasting state for the parent drug. PK parameters for the N-methyl metabolite in the fed state showed a similar pattern except for the fed state $t_{1/2}$ which was shorter than in the fasting state. Although the calculated 90%

confidence limits for AUC₀₋₂₄ of STI571, AUC₀₋₂₄ of CGP74588 and AUC₀₋₂₄ of CGP74588 lie outside the range of 80-125%, the applicant concluded that the differences in PK observed after food are not of potential clinical significance.

	Parameter	N	Ratio	90% Confidence-Interval
STI571	AUC ₀₋₂₄	10	93.0	79.0-109.5
	C _{max}	10	88.7	76.8 – 102.4
CGP 74588	AUC ₀₋₂₄	10	88.8	76.0-103.8
	C _{max}	10	84.2	70.7 – 100.3

It was difficult to observe changes in the pharmacokinetic behavior of STI571 once patients were at steady state. A better approach would have been to design a single dose crossover study in healthy volunteers with adequate washout periods. In the clinical trials, the patients were required to take Gleevec with food, and in the package insert similar recommendation is provided.

9. What is the permeability of STI571?

DPEI made a consult to DPQR pertaining to STI571 transport studies in Caco-2 cell monolayers. The conclusions are as follows.

- STI571 is a drug subject to efflux mechanisms and possibly active transporters.
- The Caco-2 studies were conducted at the concentration range of 1 to 50 μM. The Caco-2 permeability was found to be 0.95 x 10⁻⁶ cm/sec at 1μM and 7.9 x 10⁻⁶ cm/sec at 50 μM. The permeability values are consistent with the applicant's finding that STI571 is a substrate of an efflux pump where the permeability increases with increasing concentration. Based on the data and at the specific concentration range, the OTR/DPQR agreed with the applicant and concluded the STI571 was a low permeability compound.
- The dose strength of STI571 is 100 mg per capsule and the clinical dose is around 400 mg. According to the BCS guidance, this is equivalent to the concentration of 810 μM (dose strength) and 3239 μM (clinical dose) based on the molecular weight of 494 and BCS volume of 250 mL. At this high concentration, STI571 is expected to be a high permeability compound.

See APPENDIX III for detailed consult report.

10. Is there any formulation change during drug development?

The formulation changes made during the drug development are shown in the following table.

	5mg	25mg	50mg	50mg	50mg	50mg	100mg	100mg	100mg
	3752409	3752383	3752417	3752417	3752417	3752417	3752425	3752425	3752425
	00.001	00.001	00.001	00.002	00.003	00.004	00.001	00.002	00.003
STI 571									
Microcrystalline cellulose									
Crospovidone									

Silica, colloidal anhydrous/colloidal silicon dioxide									
Magnesium stearate									
Capsule contents									
Size 1, light yellow to orange yellow									
Size 1, orange to grayish orange, red inkbar									
Size 1, orange to grayish orange, red imprint NVR/SI									
Size 2, light yellow to orange yellow									
Size 3, light yellow to orange yellow									
Size 3, light yellow to orange yellow, red inkbar									
Size 3, light yellow to orange yellow, red imprint NVR/SI									
Total capsule weight	130	215	240	163	163	163	304	306	306
* corresponds to 5, 25, 50 or 100mg base, respectively									

It is noted that the non-commercial formulations (3752383.00.001 and 3752417.00.001) for 25mg and 50mg strengths have been used in the clinical studies 03 001 (PK study), 0102 and 0109 (pivotal phase 2 studies). However, based on the drug supply, less than 5% of patients used these formulations in the pivotal trials 0102 and 0109. Therefore, the formulation change may not have significant impact in the overall safety and efficacy assessment of the drug in the pivotal trials.

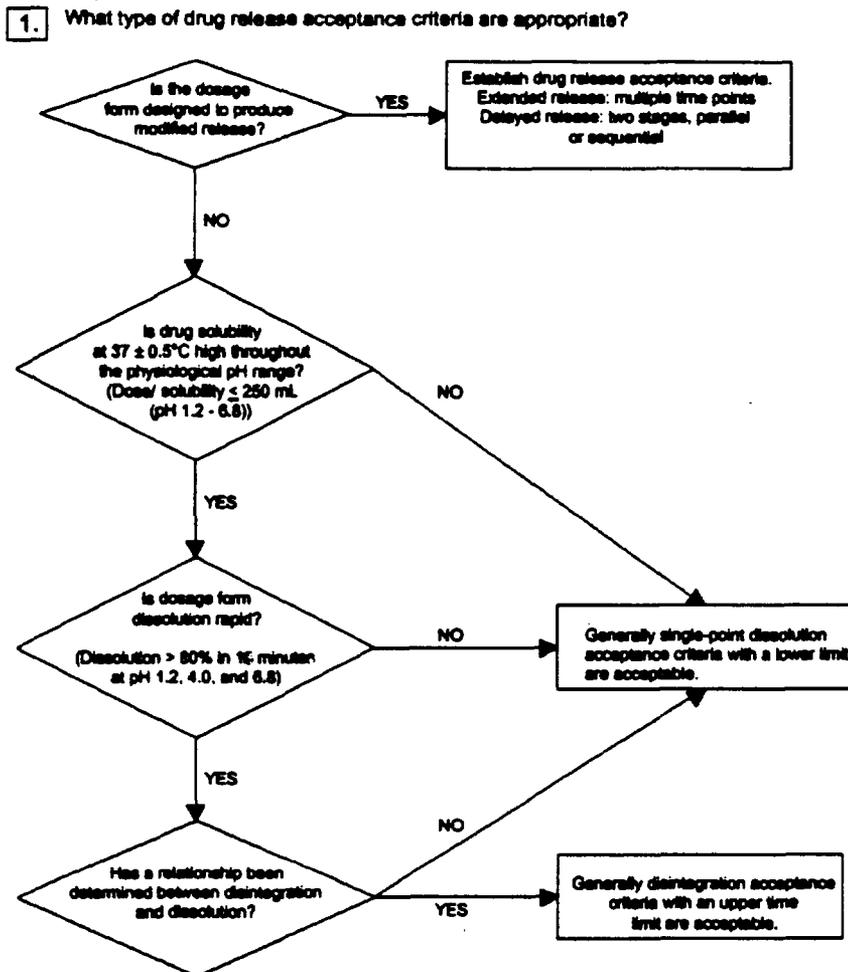
11. Is the replacement of dissolution testing with disintegration time acceptable?

The applicant proposed to test the dissolution of the first ten ST1571 50 mg and 100 mg capsule production size batches at release. If the batch data confirm the results obtained during development, the dissolution testing will be replaced by the determination of the disintegration time according to Ph. Eur./USP for release, with the following limit: "not longer than 10 minutes". The dissolution test will be maintained for stability testing of the drug product.

However, based on the ICH Guideline Q6A "Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: Chemical substances", replacement of dissolution testing by disintegration is allowed only when the criteria as set out in the decision tree #7 of this guideline (shown in the following chart) are met:

- Rapid dissolution (> 80% in 15 minutes) at pH 1.2, 4.0 and 6.8.
This criterion is fulfilled.
- High drug solubility at 37±0.5 °C throughout the physiological pH range (Dose/solubility ≤250ml at pH range 1.2-6.8).
ST1571 mesylate is freely soluble up to pH 5.5, then, solubility reduces at higher pH values. The experiment was possibly conducted at room temperature.
- A relationship between disintegration and dissolution is determined.
A correlation between disintegration and dissolution data has not been determined.
Therefore, The replacement of dissolution testing by disintegration time is not acceptable.

Decision Tree #7



V. COMMENTS:

Phase 4 Commitment:

1. In vitro studies suggest that both STI571 and its major active metabolite are potent inhibitors of CYP2D6 isoenzyme. The impact of CYP2D6 inhibition by STI571 on the pharmacokinetics of drugs that are substrates of CYP2D6 is unknown. Currently, no dosage recommendation can be made for patients who will be taking drugs that are substrates of CYP2D6. Therefore, the applicant should assess potential drug interaction between imatinib and a substrate of CYP2D6. Please submit your study protocol for review.
2. Gleevec is predominantly metabolized by the liver and eliminated through the biliary route. Since there is no clinical study conducted with Gleevec in patients with liver impairment, no specific advice regarding dosing adjustment can be given to patients with liver function

insufficiency. Therefore, the applicant should conduct a pharmacokinetics study with Gleevec in subjects or patients with liver impairment. Please submit your study protocol for review.

3. The contribution of the major metabolite of STI 571, N-demethylated piperazine derivative, in the overall pharmacologic or toxic effect of Gleevec could not be assessed. Although the AUC of the major metabolite was 16% of the parent drug, low plasma protein binding of this metabolite could potentially play a role in the overall pharmacologic or toxic effect of Gleevec. Therefore, the applicant should assess the plasma protein binding of the N-demethylated piperazine derivative of STI571.

General:

1. The most important drawback of the submission is the lack of sound rationale for the dosing strategy. The available database does not permit derivation of an 'optimal' dose or concentration. The reviewer's analyses suggests the hypothesis that the 400 mg and 600 mg produce identical effects cannot be rejected. Further, the manifestation of edema appears to be concentration - dependent, particularly when the concentration is above ~ 4 mg/L. This aspect should be taken into account to optimize the dosing strategy of imatinib. Ongoing and future clinical trials should try to target particular concentrations below, equal to and above 4 mg/L and analyze the data to test if lower concentrations produce similar effectiveness as higher concentrations but with a better safety profile.
2. The population pharmacokinetic analysis is not acceptable. The comments regarding the analysis was sent to the applicant and included in the pharmacometrics review in Appendix IV.
3. The study regarding drug interaction with ara-C and pediatric study were planned and are ongoing. Upon completion of the study, reports should be submitted to the Agency for review and proper labeling update.
4. A preliminary report of study regarding the drug interaction between imatinib and simvastatin was provided in this NDA with data from nine patients. The final study report with all (twenty) patients should be submitted for Agency review.
4. The applicant performed the food effect study of Gleevec while patients were at steady state. It is difficult to assess true effect of food on the bioavailability and pharmacokinetics of a drug once patients are at steady state. A single dose crossover study in healthy volunteers with adequate washout periods would have been more appropriate to characterize the impact of food on the bioavailability of STI571. Since the patients are required to take Gleevec with food, no food effect study is recommended.
5. The dissolution specifications are set as follows.

Dissolution conditions:

Apparatus: Basket method (Apparatus 1)

Speed: 100 rpm

Test medium: 0.1 N hydrochloric acid

Volume: 1000 mL

Temperature: 37 ± 0.5 °C

Q value not less than 80 % of the declared content dissolved in 15 minutes.

6. The applicant proposed to test the dissolution of the first ten STI571 50 mg and 100 mg capsule production size batches at release and if the batch data confirm the results obtained during development, the dissolution testing will be replaced by the determination of the disintegration time. This replacement of dissolution testing is not acceptable based on the following reasons.
 - High drug solubility at 37 ± 0.5 °C throughout the physiological pH range (Dose/solubility ≤ 250 ml at pH range 1.2-6.8) has not been established.
 - A relationship between disintegration and dissolution has not been determined.

Labeling:

1. The following changes should be made in the "CLINICAL PHARMACOLOGY" section:

CLINICAL PHARMACOLOGY

Draft Labeling

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the approval package consisted of draft labeling

Draft Labeling

VI. RECOMMENDATION:

From the Clinical Pharmacology and Biopharmaceutics perspective, ~~the~~ NDA is acceptable. However, the applicant should commit to the phase 4 studies requested in this review.

Please forward the Phase 4 commitments, general, and the labeling comments to the applicant.

/S/

John Duan, Ph.D.
Reviewer
Division of Pharmaceutical Evaluation I

Date

/S/

Joga Gobburu, Ph.D.
Pharmacometrics Reviewer
Division of Pharmaceutical Evaluation I

Date

/S/

Atiqur Rahman, Ph.D.
Team Leader
Division of Pharmaceutical Evaluation I

Date

cc: Orig 21,335
 HFD-150 Division File
 HFD-150 AStaten, MCohen, JJohnson
 HFD-860 MMehta, ARahman, JDuan
 HFD-340 Vishwanathan
 CDR

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the approval package consisted of draft labeling

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APPENDIX II. INDIVIDUAL STUDY SYNOPSIS

1. Dose finding Study 01 003.

Volume 1.37

Study title: A phase I, dose-finding study to determine the safety, tolerability, pharmacokinetic and pharmacodynamic profiles and to evaluate for preliminary anti-leukemic effects of STI571 in patients with chronic myeloid leukemia (CML) resistant to interferon-alpha (IFN).

Investigator & location: Brian J. Druker, MD; Charles L. Sawyers, MD; Moshe Tolpaz). Center 001: Oregon Health Sciences University, Portland, Oregon; Center 002: UCLA Medical Center, Los Angeles, California; Center 003: MD Anderson Cancer Center, Houston Texas.

Study period: June 22, 1998 to May 06, 2000

Study formulation: STI571 was supplied as 5, 25, 50, and 100 mg hard gelatin capsules for oral administration with following formulation control and batch numbers.

STI571	Formulation Control No.	Batch No.
5 mg	3752409.00.001	B970111
25 mg	3752383.00.001	B970083
50mg	3752417.00.001, 3752417.00.002, 3752417.00.003	B970084, X356 0999, X362 1199
100 mg	3752425.00.001, 3752425.00.002	B970085, B990026, B990034, X365 1199, X024 0100

Objectives:

To evaluate the basic PK characteristics of STI571 and its metabolite (CGP 74588).
To assess the plasma concentrations and PK behavior after single and multiple doses
To examine the relationship between dose and drug exposure (AUC) and drug effect.

Subjects: Seventy patients participated in the study (64 adults and 6 children).

Study Design:

This is an open-label study carried out in 70 patients. Adult patients received 25, 50, 85, 140, 200, 250, 300, 350, 400, 500, 600, 750, 800 or 1000 mg daily, and patients <18 years received 175 mg/m² (doses of 125, 150, 200, 225, 425, and 425 mg daily). For the once daily dose regimen, blood samples were collected on Day 1 at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 24 hours after drug administration. At steady state blood samples were collected at 0.5, 1, 1.5, 2, 3, 4, 8, 24, 32 and 48 hours after drug administration. A 24 hour treatment-free period was maintained at steady-state after the 24 hour sampling for determination of terminal phase pharmacokinetic variables during the 32 and 48 hour steady-state measurements. For the b.i.d dose regimen (800 and 1000 mg total daily doses), blood samples were collected at 0, 1, 2, 3, 4, and 10 hours after the first dose (prior to the second dose), and 12, 13, 16, 24, 32, and 48 hours (after the second dose), both on day 1 and at steady-state. A 24 hour treatment-free period was maintained at

steady state after the 24 hour sampling for determination of terminal phase pharmacokinetic variables during the 32 and 48 hour steady-state measurements. The non-compartmental PK parameters C_{max} , t_{max} , λ_z , $t_{1/2}$, AUC_{0-24} , $AUC_{0-\infty}$, V_z/F , Cl/F , and accumulation ratio R_A were calculated from the plasma concentration-time profile. PK parameters at steady-state in relation to WBC reduction was analyzed.

Hematologic and bone marrow assessments were performed to detect anti-leukemic effects. WBC and platelet counts were used to determine complete hematologic response (CHR) in adults with chronic phase CML. Bone marrow examinations and cytogenic assessments were used to determine CHR and bone marrow response in patients with advanced Ph+ leukemias. Safety and tolerability were assessed by recording all adverse events reported or observed during the course of the treatment and by monitoring the results of standard clinical laboratory investigations, physical examinations, ECG and vital signs recordings throughout the study period.

Results:

Assay performance:

STI571 and CGP74588 were determined performed on

The analyses were

prepared using

The validation results are shown in the following table.

Samples were

Species	Range (ng/mL)	QC standard
STI571	8.53-10.7	95.8-99.0
CGP74588	7.6-12.8	95.5-101

The assays are acceptable based on the current standards. However, there were two methods that have been used, but only one validation data set is presented in the report.

Pharmacokinetics:

STI571 was rapidly absorbed after oral administration with C_{max} being observed at about 2-4 hours post-dose. The C_{max} ranged from 72 ng/ml (at 25 mg) to 3395 ng/ml (at 600 mg) after once daily administration and from 2315 ng/ml (at 800 mg) to 3380 ng/ml (at 1000 mg) after twice daily administration as shown in the following tables and figures.

Table. PK parameters of STI571 in patients on Day 1 of administration

Dose/day mg (n)		t_{max} (h)	C_{max} (ng/ml)	λ_z (/h)	$t_{1/2}$ (h)	AUC_{0-24} ($\mu\text{g}\cdot\text{h}/\text{ml}$)	$AUC_{0-\infty}$ ($\mu\text{g}\cdot\text{h}/\text{ml}$)	V_z/F (L)	CL/F (L/h)
25 (3)	Mean	2.2	71.6	0.056	12.7	0.7	1.0	461.6	24.8
	SD	0.8	17.9	0.008	1.8	0.2	0.2	172.0	6.0
50 (3)	Mean	1.8	185.6	0.090	10.1	1.4	1.91.9	377.2	28.3
	SD	1.0	56.6	0.065	5.1	0.3	0.50.5	145.9	7.7
85 (4)	Mean	2.0	444.7	0.064	11.7	4.3	5.8	261.7	16.3
	SD	1.4	209.2	0.023	3.6	1.6	2.6	82.7	5.2
140 (3)	Mean	1.8	889.3	0.053	13.3	8.9	12.3	306.8	16.1
	SD	1.0	757.7	0.006	1.5	6.9	9.1	183.0	10.3
200 (3)	Mean	4.0	846.0	0.045	18.9	11.0	21.5	273.3	12.7
	SD	3.6	197.1	0.022	11.6	3.7	16.3	66.3	6.7
250 (4)	Mean	2.6	1381.4	0.068	11.6	18.7	26.5	182.1	10.3
	SD	1.1	366.3	0.033	4.1	7.2	9.6	93.4	3.0
300 (5)	Mean	2.6	1640.0	0.052	13.8	19.0	27.4	237.2	12.1
	SD	2.1	443.0	0.009	2.3	7.3	11.5	68.0	3.7
350 (3)	Mean	2.5	1190.0	0.049	14.4	13.8	20.6	353.0	17.1
	SD	0.9	150.0	0.007	2.1	1.4	2.3	36.7	2.0
400 (4)	Mean	3.1	1907.5	0.051	14.8	24.8	38.8	236.0	12.5
	SD	2.0	355.0	0.016	5.8	7.4	15.9	76.5	7.2
500 (6)	Mean	3.8	2056.7	0.050	14.7	28.5	45.3	265.9	14.1
	SD	2.1	605.4	0.014	3.6	10.7	20.5	88.1	8.3
600 (7)	Mean	2.9	3395.0	0.066	10.9	39.7	52.4	245.5	16.6
	SD	1.4	2408.9	0.012	2.0	25.9	33.7	152.4	11.9
750 (6)	Mean	3.7	3016.5	0.072	10.6	34.4	45.6	279.6	18.9
	SD	2.3	1040.2	0.025	3.4	13.2	21.6	127.0	6.9

b.i.d regimen

800 (4)	Mean	14.0	2315.3	0.040	16.7	36.2	66.3	304.9	12.5
	SD	2.3	635.7	0.010	3.7	7.4	12.3	116.3	2.8
1000 (6)	Mean	12.2	3379.7	0.070	11.1	51.0	81.7	226.6	15.8
	SD	4.8	1547.4	0.030	3.4	22.7	38.7	106.3	9.5

Pediatric patients

125 (1)		3.0	2260.0	0.130	5.3	18.2	19.3	50.0	6.5
150 (1)		3.0	1640.0	0.060	11.0	19.9	25.9	92.1	5.8
200 (1)		2.0	3612.0	0.200	3.5	23.2	23.5	43.5	8.5
225 (1)		3.0	2586.0	0.050	14.7	36.7	56.8	84.2	4.0
425 (2)	Mean	3.5	3503.5	0.070	10.0	42.3	58.4	165.7	10.8
	SD	0.7	3413.2	0.010	1.5	47.1	47.1	149.7	8.7

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Figure. Mean plasma concentrations on Day 1 after oral administration of STI571 at doses from 25 mg to 750 mg

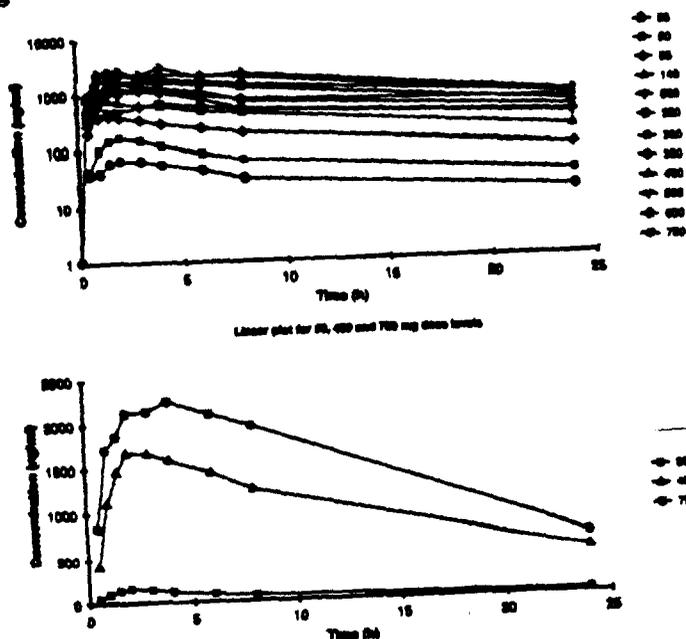


Table. PK parameters of STI571 in patients at steady state following once daily oral administration

Dose/day mg (n)		t_{max} (h)	C_{max} (ng/ml)	λ_z (/h)	$t_{1/2}$ (h)	AUC_{0-24} ($\mu\text{g}\cdot\text{h}/\text{ml}$)	$AUC_{0-\infty}$ ($\mu\text{g}\cdot\text{h}/\text{ml}$)	V_z/F (L)	CL/F (L/h)
25 (3)	Mean	1.0	179.9	0.050	14.5	1.9	2.7	345.3	16.5
	SD	0.5	89.2	0.000	0.7	0.9	1.4	214.5	10.0
50 (3)	Mean	3.8	365.7	0.050	15.1	4.6	7.0	239.6	10.9
	SD	3.6	75.6	0.010	3.3	0.4	0.5	70.7	1.0
85 (3)	Mean	2.2	799.6	0.040	19.4	9.8	16.1	254.2	9.3
	SD	1.4	463.1	0.010	4.1	3.3	5.6	70.9	3.1
140 (3)	Mean	1.7	1053.8	0.030	23.3	12.1	21.4	391.2	11.7
	SD	0.3	236.3	0.010	10.3	1.4	3.4	166.3	1.4
200 (4)	Mean	3.8	1026.7	0.050	14.7	12.9	19.2	393.7	18.2
	SD	2.9	572.9	0.000	1.6	6.1	8.9	187.1	7.8
250 (6)	Mean	2.1	1548.3	0.040	18.7	19.8	33.5	355.7	13.3
	SD	1.2	507.6	0.010	2.8	5.2	9.0	95.6	3.0
300 (6)	mean	6.4	1834.2	0.040	16.7	27.4	48.5	303.2	13.0
	SD	8.8	668.4	0.010	2.0	11.5	29.0	119.4	6.4
350 (5)	mean	3.1	1407.0	0.050	17.3	20.0	38.1	542.8	31.1
	SD	1.0	710.7	0.030	6.2	10.6	23.0	261.2	35.5
400 (5)	mean	3.3	2596.0	0.040	19.3	40.1	81.9	295.0	11.2
	SD	1.1	786.7	0.010	4.4	15.7	45.0	62.5	4.0

Dose/day mg (n)		t_{max} (h)	C_{max} (ng/ml)	λ_z (/h)	$t_{1/2}$ (h)	AUC_{0-24} ($\mu\text{g}\cdot\text{h}/\text{ml}$)	$AUC_{0-\infty}$ ($\mu\text{g}\cdot\text{h}/\text{ml}$)	Vz/F (L)	CL/F (L/h)
500 (9)	mean	4.0	2808.1	0.040	19.8	41.9	81.1	363.6	13.3
	SD	1.6	940.5	0.010	7.0	14.5	37.6	134.3	4.7
600 (9)	mean	3.1	3508.9	0.050	15.6	51.7	89.9	296.9	14.4
	SD	1.1	1649.3	0.010	5.0	26.7	74.2	102.5	6.8
750 (6)	mean	3.3	3804.8	0.050	15.0	56.4	85.4	324.6	14.7
	SD	1.0	1488.7	0.010	3.5	20.2	34.6	145.3	4.8

b.i.d regimen

600 (4)	mean	2.3	2325.0	0.040	17.5	37.2	66.6	414.2	17.0
	SD	1.3	561.2	0.010	3.5	9.8	27.8	40.9	4.3
800 (4)	mean	7.8	3701.8	0.040	19.6	68.4	138.8	386.5	13.3
	SD	7.4	1433.5	0.000	2.6	29.8	53.8	179.2	5.0
1000 (5)	Mean	9.8	4478.0	0.050	17.0	82.5	174.1	386.02	16.44
	SD	9.8	2144.6	0.020	5.4	42.3	105.8	290.16	12.02

Pediatric patients

125 (1)		3.00	2370.00	0.030	25.61	21.8	33.8	211.68	5.73
150 (1)		3.00	3840.00	0.080	9.17	49.3	59.9	40.31	3.05
200 (1)		2.00	4151.00	0.040	16.74	34.2	40.7	141.42	5.86
225 (1)		4.00	1600.00	0.040	16.00	20.7	31.3	250.77	10.87
425 (2)	mean	3.00	4654.50	0.04	17.44	64.1	106.3	196.63	7.63
	SD	0.00	2071.12	0.00	1.60	32.9	50.9	116.13	3.91

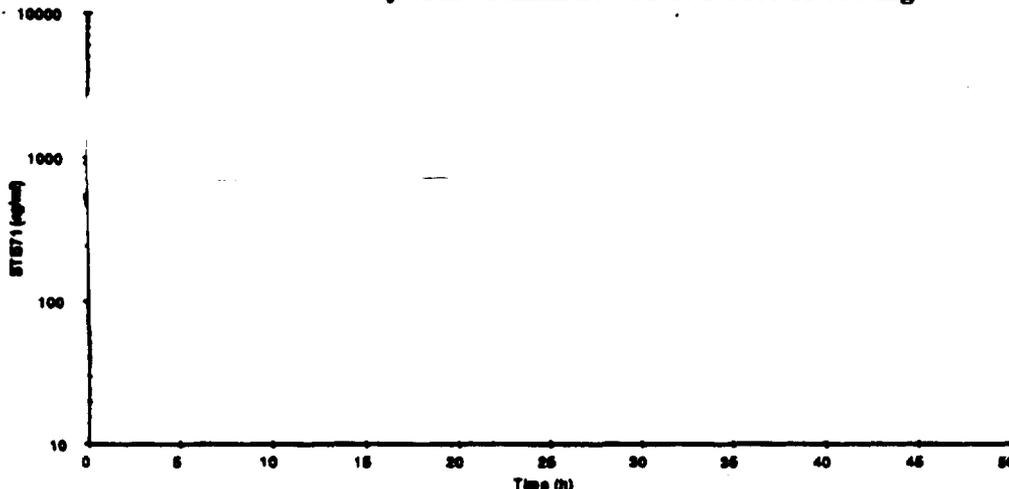
The following table provides a comparison of the main PK parameters for STI571 on Day 1 and at steady state. The comparison of AUC_{0-24} reveals a 1.5 - 3 fold drug accumulation after once daily dosing. In addition, the mean $t_{1/2}$ at steady state appears longer though this may have been due to the fact that the sampling schedule on Day 1 was too short to determine the true $t_{1/2}$. The last blood sample on Day 1 was taken only 24 hours after drug administration whereas at steady state the profiles included samples taken at 48 hours.

Table. Comparison of PK parameters on Day 1 and at steady state mean (SD)

Dose/day (mg)	$t_{1/2, \text{day 1}}$ (h)	$t_{1/2, \text{ss}}$ (h)	$AUC_{\text{ss}}/AUC_{\text{d1}}$	$C_{\text{max, ss}}/C_{\text{max, d1}}$
25	12.66 (1.79)	14.50 (0.67)	2.41 (0.73)	2.43 (0.80)
50	10.11 (5.12)	15.12 (3.29)	3.28 (0.64)	2.03 (0.35)
85	11.74 (3.63)	19.42 (4.13)	2.11 (0.09)	1.67 (0.25)
140	13.32 (1.51)	23.31 (10.31)	1.95 (1.30)	1.99 (1.76)
200	18.90 (11.56)	14.73 (1.56)	1.25 (0.86)	1.23 (0.68)
250	11.59 (4.14)	18.66 (2.79)	1.26 (0.44)	1.26 (0.40)
300	13.78 (2.30)	16.69 (2.02)	1.69 (0.59)	1.26 (0.61)
350	14.39 (2.08)	17.25 (6.24)	1.75 (0.61)	1.42 (0.46)
400	14.79 (5.79)	19.31 (4.37)	1.51 (0.57)	1.14 (0.36)
500	14.69 (3.64)	19.81 (7.02)	1.46 (0.46)	1.29 (0.29)
600	10.85 (2.03)	15.60 (5.01)	2.22 (2.79)	1.72 (1.97)
750	10.63 (3.35)	15.02 (3.50)	1.70 (0.45)	1.29 (0.36)
800	16.69 (3.72)	19.63 (2.55)	1.89 (0.76)	1.68 (0.70)
1000	11.13 (3.39)	16.98 (5.44)	1.76 (0.70)	1.52 (0.98)

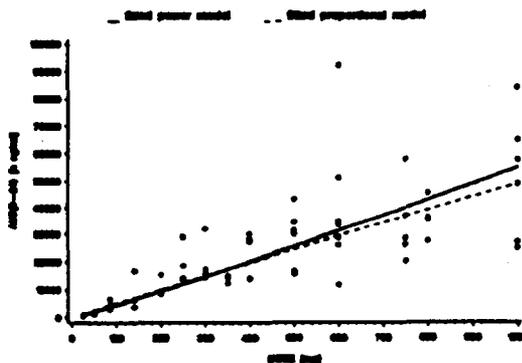
A comparison of the Day 1 and Day 28 PK profiles for STI571 in a representative patient treated at 400 mg daily (No 01/16) is given in the following Figure.

Figure. Plasma concentrations of STI571 in Patient 01/16 on Days 1 and 28 after once daily oral administration at a dose of 400 mg



A drug-interaction was observed involving the induction of metabolism of STI571. A patient (01/14) treated at a dose of 350 mg daily failed to respond hematologically and was found to have inappropriately low plasma levels of STI571 (AUC_{0-24} of $3.7 \mu\text{g}\cdot\text{h}/\text{ml}$ in contrast to a mean AUC_{0-24} of $20 \mu\text{g}\cdot\text{h}/\text{ml}$ for other patients treated at 350 mg). The patient was receiving phenytoin, an anticonvulsant which is a potent inducer of liver P450 isoenzyme. The patient promptly responded when phenytoin was stopped, though simultaneous dose escalation of STI571 to 500 mg was also performed.

The relationship between dose and exposure was investigated on Day 1 and at steady state. As depicted in the following Figure, the increase in mean plasma AUC was proportional to the

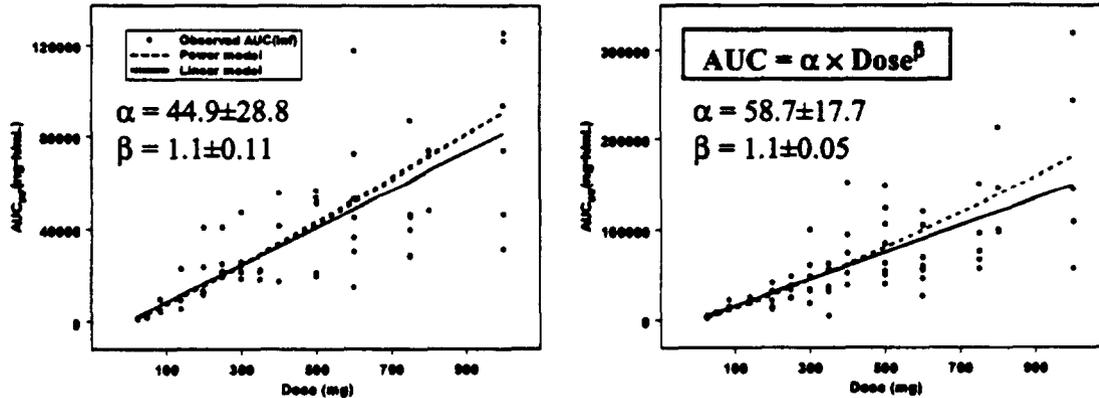


administered dose. The analyses showed that the power model was adequate and 90% confidence intervals for the parameter were either close to 1 (at Day 1) or included 1 (at steady state). Therefore, dose-proportionality of the AUC was established for the dose range of 25 mg to 1000

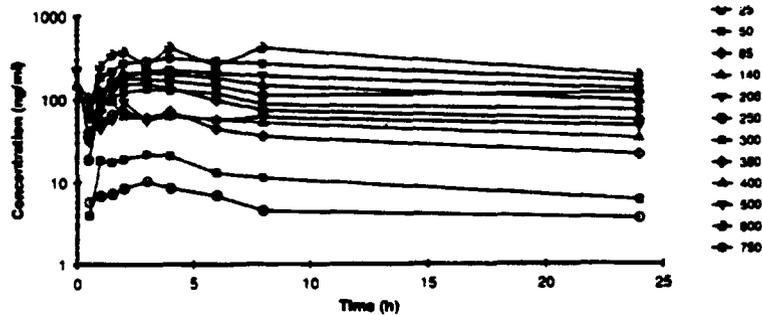
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mg, even though the 800 and 1000 mg daily doses were administered as divided doses.

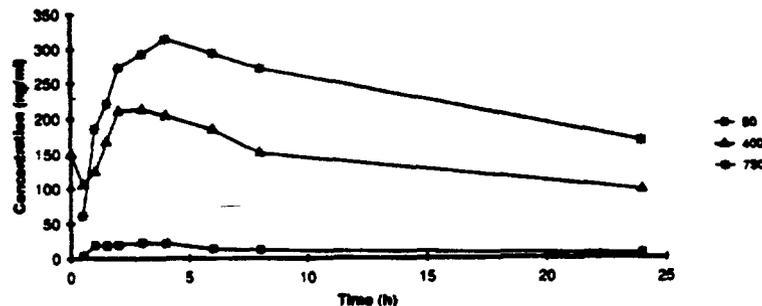
Since the applicant only examined the dose proportionality by using the AUC_{0-24} data on day 1 and at steady state, the reviewer verified the dose proportionality by fitting the $AUC_{0-\infty}$ data to a power model with a proportion error model. Similar results were obtained as shown in the following figure. The left panel shows the results on Day 1 and the right at steady state.



The main metabolite of STI571 in human liver S12 fractions *in vitro* was CGP 74588, the desmethyl derivative of the parent compound. CGP 74588 is also pharmacologically active. The terminal elimination of the metabolite was longer ($t_{1/2}$ 27-58 hours at steady state). There was also greater inter- and intra-patient variability in the PK parameters of CGP 74588 when



Linear plot for 80, 400 and 750 mg dose levels



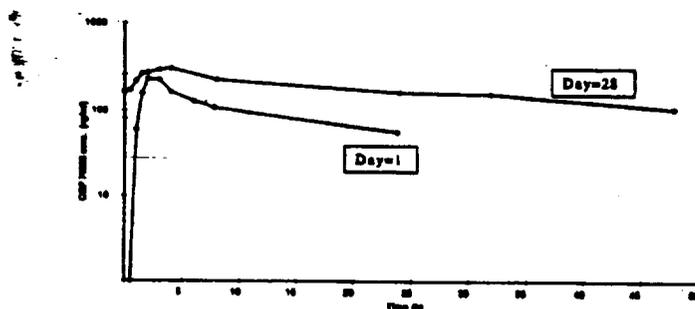
compared to the parent compound. This variability may be due to quantitative variations in

CYP3A4 levels, the major cytochrome P450 isoenzyme involved in the microsomal biotransformation of STI571. In most patients, CGP 74588 could be detected in plasma 30 minutes (first sampling time) after oral administration of parent compound. The PK parameters of CGP74588 derived from the plasma concentration time curves on Day 1 (the Figures) are shown in the table below.

Table. PK parameters of CGP 74588 in patients on Day 1 of administration of STI571

Dose/day mg (n)		t_{max} (h)	C_{max} (ng/ml)	λ_z (/h)	$t_{1/2}$ (h)	AUC_{0-24} ($\mu\text{g}\cdot\text{h}/\text{ml}$)	$AUC_{0-\infty}$ ($\mu\text{g}\cdot\text{h}/\text{ml}$)
25 (3)	mean	4.0	10.8	0.094	15.2	0.1	0.2
	SD	1.7	5.5	0.104	10.8	0.1	0.1
50 (3)	mean	2.7	25.3	0.077	16.4	0.2	0.4
	SD	0.6	12.7	0.081	10.7	0.1	0.1
85 (4)	mean	3.0	85.7	0.058	14.4	0.8	1.2
	SD	1.2	53.1	0.034	5.4	0.5	0.7
140 (3)	Mean	3.5	75.3	0.030	26.1	1.1	2.5
	SD	3.9	46.7	0.013	12.0	0.7	1.4
200 (3)	Mean	4.0	113.5	0.040	21.5	1.3	2.6
	SD	3.5	77.6	0.026	10.1	0.1	0.3
250 (4)	Mean	3.0	204.6	0.055	16.8	3.2	5.3
	SD	0.8	113.4	0.040	7.9	2.0	2.4
300 (5)	Mean	3.2	151.4	0.028	25.5	2.3	5.2
	SD	1.9	32.3	0.005	4.5	0.7	2.1
350 (5)	Mean	2.7	163.7	0.034	23.2	1.9	4.0
	SD	1.2	43.1	0.014	10.9	0.4	1.8
400 (4)	Mean	2.4	235.5	0.044	17.8	3.2	5.6
	SD	1.1	16.2	0.021	6.5	0.6	2.3
500 (6)	Mean	4.4	258.5	0.030	29.1	4.1	10.6
	SD	2.3	77.7	0.016	13.8	1.6	6.2
600 (7)	Mean	4.1	469.7	0.038	20.0	7.0	12.7
	SD	1.9	409.5	0.010	7.2	6.4	11.0
750 (6)	Mean	4.0	437.7	0.042	19.7	5.6	10.6
	SD	2.1	179.7	0.021	7.6	2.8	6.8
b.i.d regimen							
800 (4)	mean	8.5	230.1	0.020	32.5	4.1	12.6
	SD	6.6	33.1	0.010	9.4	0.5	2.8
1000(6)	mean	17.7	450.9	0.030	21.3	7.6	16.5
	SD	5.1	237.2	0.010	7.3	4.2	8.0
Pediatric patient^a							
125 (1)		4.0	224.0	0.070	9.3	2.6	3.3
150 (1)		6.0	127.0	0.020	28.7	2.3	5.5
200 (1)		2.0	813.5	0.120	5.6	7.2	7.6
225 (1)		4.0	243.0	0.030	23.1	4.1	8.5
425 (2)	Mean	5.5	516.6	0.030	20.1	8.4	18.6
	SD	3.5	514.2	0.000	1.7	9.9	18.3

A comparison of the Day 1 and Day 28 PK profiles for CGP 74588 in a representative patient (No 01/16) treated with 400 mg daily of STI571 is given in the following Figure.



After repeated administration, there was a 4-7-fold accumulation of metabolite at steady state following once daily dosing which was greater than that of parent drug. The increase in mean AUC and C_{max} in plasma was over-proportional to the administered dose, with some inter-patient variability.

The mean CGP74588/STI571 AUC ratio following both once daily dosing of 25 mg and twice daily dosing of 1000 mg was 0.14, indicating a limited contribution of metabolite exposure to total drug activity.

Conclusions:

1. The distribution and elimination of STI571 was multi-phasic with an apparent terminal half-life ($t_{1/2}$) averaging 10-23 hours.
2. Exposure (AUC) for parent drug was dose-proportional for the dose range of 25-1000 mg.
3. The main metabolite of STI571 was CGP 74588, the desmethyl derivative of the parent compound. CGP 74588 is pharmacologically active. The terminal elimination of the metabolite was longer ($t_{1/2}$ 27-58 hours at steady state). There was also greater inter- and intra-patient variability in the PK parameters of CGP 74588 when compared to the parent compound.
4. The comparison of AUC_{0-24} of parent drug at steady-state and on Day 1 revealed a 1.5-3 fold drug accumulation after repeated once daily dosing. For the major metabolite CGP74588, there was a 4-7-fold accumulation at steady state following once daily dosing.

Comments:

1. There were two assay methods that have been used. However, only one validation data set is presented in the report.
2. There was considerable inter-patient variability of absorption. The reason was postulated to be due, in part, to variation in protein binding between patients. However, variation in protein binding between patients is not adequately addressed in the submission.
3. Drug interaction was evidenced by decreased efficacy with coadministration of phenytoin. Effect of cytochrome P450 enzyme induction on the pharmacokinetics of Gleevec should be studied.

2. Mass Balance Study

Volume 1.39

Study title: A study to assess the absorption, disposition, kinetics and biotransformation of radiolabelled drug and metabolites after a single oral dose of 200 mg [^{14}C]STI571 to healthy volunteers.

Investigator & location:

Study period: Nov. 04, 1999 to Nov. 10, 1999

Study formulation: [^{14}C]STI571 (methanesulfonic acid salt) from DMPK(CH), Isotope Laboratory, Novartis Pharma AG, Basel. Radiolabelled batch No. 7524509 (synthesis batch no. RSE052-2). Radiolabel in 2-position of pyrimidine ring. Specific radioactivity: 4.991 kBq/mg (0.135 $\mu\text{Ci}/\text{mg}$). Radiochemical purity: 100%. Single doses of [^{14}C]STI571 (salt) were weighed into hard gelatin capsules (batch no. X3280999, by Isotope Laboratory and PHAD Basel).

Objectives:

- To determine the rate and routes of excretion and the mass balance in urine and feces;
- To determine the kinetics of STI571, total radioactivity and metabolites in blood/plasma
- To identify and quantify the metabolites in plasma, urine and feces
- To investigate the biotransformation pathways
- To evaluate the absorption, if feasible
- To determine the essential clearance mechanisms of STI571, if feasible

Subjects: Four healthy Caucasian male subjects, age 40-60 years, body weight within +15% of ideal body weight, screening passed within 3 weeks prior to first dose. Subjects were genotyped for CYP2D6 activity and none were poor metabolizers.

Study Design:

Four subjects received a single oral dose of 200 mg [^{14}C]STI571 (base =239 mg methanesulfonic acid salt; 1.18 MBq ^{14}C (=32 μCi)) in hard gelatin capsule. The nominal observation period after the single dose was 7 days. Blood, urine and feces were collected. Feces collection was continued in three subjects until day 12.

For plasma concentrations of STI571, CGP74588 and total ^{14}C -radioactivity, the parameters $\text{AUC}_{0-\infty}$, AUC_{inf} , C_{max} , t_{max} , $t_{1/2}$, V_z/f and CL/f were determined. From urine and feces concentrations of ^{14}C -radioactivity, the cumulative excretion (dose proportions) per sample and the total excretion (mass balance) were determined. AUC of metabolites in plasma and balance of metabolites in excreta were determined. The chemical structures of main metabolites were identified by LC-MS.

The analytical methods used were as follows.

- 2.
- 3.
- 4.

Results:

Assay performance:

STI571 and CGP74588 were determined in plasma by LC/MS/MS. The analyses were performed on a [redacted] LC was carried out on a [redacted] in [redacted] column. Samples were prepared using solid phase extraction.

Species	Range (ng/mL)	Calibration Standard		QC standard	
		Precision (%)	Accuracy (%)	Precision (%)	Accuracy (%)
STI571					
CGP74588					

The performance of radioactivity assay is summarized in the following table.

Matrix	Levels (dpm)	Mean (±SD) of the QC samples (%)
Whole blood	158, 519, 985	93.7 ± 4.5
Plasma	108, 537, 1086	99.0 ± 5.0
Urine	198, 820, 4261	100.8 ± 4.1
Feces	381, 1810, 8372	100.8 ± 2.2

The assays are acceptable based on the current standards.

Metabolism & Pharmacokinetics:

Several mechanisms appear to contribute to the clearance of STI571, including transport as well as various metabolic pathways.

The plasma concentration profiles of various species are shown in the following figures.



The pharmacokinetic parameters are summarized in the following table.

Key Pharmacokinetic Parameters:

(Parameters for Plasma Concentrations)	AUC _{0-48h} (mean ± SD) [nmol·h/mL] ^{a,b}	AUC _{0-48h} (mean ± SD) [% of total ¹⁴ C] ^{a,b}	AUC (mean ± SD) [nmol·h/mL]	C _{max} (mean ± SD) [nmol/mL] ^a	Terminal t _{1/2} (mean ± SD) ^c [h]
¹⁴ C (total drug, i.e. including metabolites)	34.6 ± 1.7	100%	53.1 ± 2.0	2.02 ± 0.09	57.3 ± 12.5 (72-168 h)
STI571	20.0 ± 1.8	58% ± 3%	21.6 ± 2.3	1.87 ± 0.19	13.5 ± 0.9 (12-48 h)
CGP 74588 N-desmethyl metabolite	2.85 ± 0.37	8% ± 1%	3.47 ± 0.39	0.24 ± 0.05	20.6 ± 1.7 (12-48 h)
Total of 2 compounds	22.9 ± 1.9	66% ± 3%	25.1 ± 2.3	-	-

Following administration of oral dose of 200 mg, [¹⁴C]STI571, C_{max} of STI571 and the total radioactivity was reached 1 to 2 hours after dosing. No or minimal first-pass metabolism appears to occur. Two thirds of ¹⁴C-AUC_{0-48h} were covered by unchanged drug and the main metabolite CGP 74588. About one third of ¹⁴C-AUC was accounted for by minor unidentified metabolites. The extent of absorption was estimated to be approximately 70% of dose, based on the amount of dose excreted in urine, and the amount of dose excreted between 72 and 264 h in feces, and the amount remaining in the body at study termination.

The ¹⁴C-radioactivity was excreted slowly, mainly in feces. STI571 showed a low clearance, with a mean plasma half-life of 13.5 hours. Total radioactivity (sum of STI571 and metabolites) was eliminated in a multi-exponential manner with a terminal-half-life longer than two days. Excretion of radioactivity was largely with the feces (mean: 68% of dose). Renal excretion was minor (13%). The bulk of the dose was recovered within 7 days (80%). Small proportions of the dose were recovered between day 8 and day 11. After 11 days, excretion was not complete and still continued with approx. 0.6% per day.

The metabolite patterns in plasma at 2 and 8 hours after dosing showed STI571 (P1) as the main component, followed by N-desmethyl metabolite (CGP 74588). Additionally, several minor peaks might be present. The major component in feces was STI571 (20% of dose) and CGP 74588 (9%). CGP 71422 was of minor importance (3%). Other minor metabolites were detected but not identified. Fecal excretion may have been due partly to unabsorbed drug. In urine, the main radioactive compounds were STI571 (5%) and CGP 74588 (1.5%). The sum of the metabolites CGP 74588 and CGP 71422, and of other minor unidentified metabolites accounted for at least 35% of the dose in the excreta. Thus oxidative metabolism, catalyzed mainly by CYP3A, may be a major elimination mechanism.

Balance of metabolites in the excreta is shown in the following table.

Compound	Peak	Feces (0-168 h)	Urine (0-72 h)	Total of Feces and Urine
% of dose (mean ± SD, N = 4)				
CGP 71422 (piperazine-4-N-oxide)	P3*	3.4 ± 0.8	0.5 ± 0.1	3.9 ± 0.9
CGP 74588 (N-desmethyl)	P2*	9.2 ± 1.8	1.5 ± 0.4	11 ± 2
STI571	P1	20 ± 4	5.4 ± 1.7	25 ± 5
undefined peaks		15 ± 4	4.4 ± 0.9	20 ± 4
Total of Peaks/recovered ¹⁴ C		48 ± 8	12 ± 2	59 ± 9
Not recovered from 1		7.0 ± 2.3	0	7.0 ± 2.3
Not recovered from sample processing		12 ± 6	0	12 ± 6
Total analyzed in pool		66.9 ± 4.5	11.8 ± 1.5	78.8 ± 5.2
Total excreted in indicated period		66.9 ± 4.5	11.8 ± 1.5	78.8 ± 5.2
Total excreted in period 0-264 h (N=3)		67.9 ± 4.4	13.2 ± 1.6	81.1 ± 4.9

*contains an additional metabolite of STI571 of molecular mass: 509 (=M+oxygen) as shown by LC-MS.

In both feces and urine, STI571 was the main component (P1). CGP 74588 (P2, the main metabolite) and CGP 71422 (P3) were identified by LC-MS. In urine as well as in feces extract, several metabolites of STI571 with the same molecular mass of 509 (M+oxygen) were detected by LC-MS. They contributed less than 4% and 0.5% of the dose each in feces extract and urine, respectively.

CGP 53715, a potential degradation product (aromatic amine moiety of STI571) was neither detected in feces extract nor in urine by ¹⁴C and LC-MS. STI571 appeared to be stable regarding benzamide-bond hydrolysis in the gastrointestinal tract.

Conclusions:

1. This study showed the rates and routes of excretion and the mass balance in urine and feces.
2. Following administration of oral dose of 200 mg, [¹⁴C]STI571 was absorbed with C_{max} of STI571 and the total radioactivity reached 1 to 2 hours after dosing.
3. In both feces and urine, STI571 was the main component. CGP 74588 was the main metabolite.
4. The ¹⁴C-radioactivity was eliminated slowly, mainly in feces, in a multi-exponential manner with a terminal half-life longer than two days. STI571 showed a low clearance, with a mean plasma half-life of 13.5 hours. The excretion was not complete after 11 days.
5. Unchanged drug and the main metabolite CGP 74588 covered two thirds of ¹⁴C-AUC_{0-48h}. About one third of ¹⁴C-AUC was accounted for by minor unidentified metabolites.
6. Oxidative metabolism, catalyzed mainly by CYP3A, may be a major elimination mechanism.

3. Absolute Bioavailability Study

Volume 1.40

Study title:

A single-center, open-label, three-period, three-treatment, randomized, crossover study to investigate the absolute bioavailability of a single oral dose of STI571 400 mg in form of a hard gelatin capsule and STI571 400 mg oral solution compared with STI571 up to 100 mg given as an intravenous injection.

Investigator & location:

Study period: Jul 20, 2000 to Oct 28, 2000

Study formulation: STI571 was provided as 100 mg hard gelatin capsules (Formulation No. KN 3752425.00.002, Batch No. X0210100), as powder for solution (250 mg/vial) for oral use and i.v. infusion (Formulation No. KN 3758877.00.001, Batch No. Y03110200).

Objectives:

Primary objective was to investigate the absolute bioavailability of a single oral dose of STI571 400 mg in form of a hard gelatin capsule and STI571 400 mg oral solution compared with STI571 100 mg given as an intravenous injection. Secondary objective was to investigate the tolerability of intravenous doses of STI571.

Subjects: Pilot Phase: 3 subjects, Main study Phase: 12 subjects (healthy, non-smoking, males and post-menopausal or sterile females aged 40- 60 years).

Study Design:

During the pilot phase, 3 healthy volunteers received a single, 60-min. i.v. infusion of 30 mg STI571. Based on the mean plasma concentration of the parent compound at the end of the infusion, the i.v. dose level for the main study was determined.

The main study was an open-label, three-treatment, three-period, randomized crossover study. Subjects received an oral dose of 400 mg STI571 in capsule form, 400 mg STI571 as an oral solution, and 100 mg STI571 i.v. infusion in random sequences with a minimum 7-day washout phase between treatments.

Physical examination, electrocardiogram (EGG), vital signs, laboratory safety evaluations (hematology, blood chemistry, urinalysis), special laboratory evaluation (genotyping of CYP2D6), monitoring of adverse events (AEs).

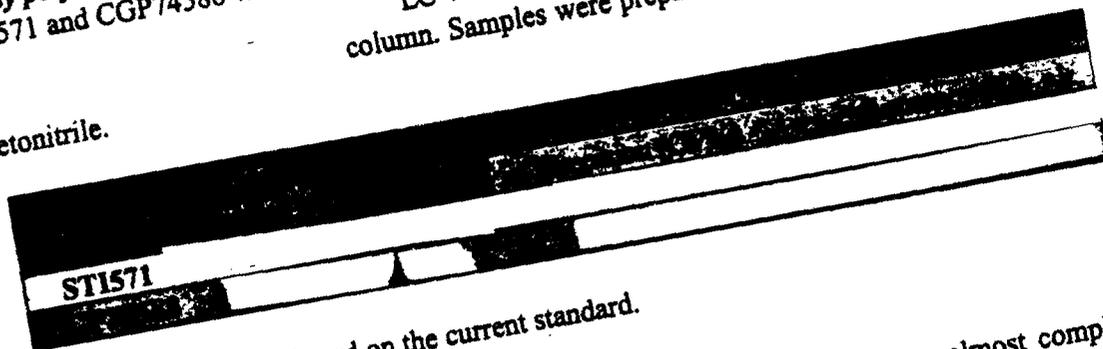
Sampling times for I.V. were 0.25, 0.5, 0.75, 1, 1.25, 1.2, 2.5, 4, 6, 12, 36, and 72 hours post dose and for oral administration were 0.5, 1, 1.2, 2.5, 4, 8, 24, 48, and 96 hours post dose. The PK profile were obtained after single administration of 400 mg STI571 as a capsule, 400 mg STI571 as an oral solution, and 100 mg STI571 as an I.V. infusion to determine absolute bioavailability, and to provide a descriptive exploratory PK analysis.

Results:

Assay performance:

STI571 and CGP74588 were determined in plasma LC/MS/MS. The analyses were performed on a LC was carried out on a column. Samples were prepared using protein precipitation with

acetonitrile.

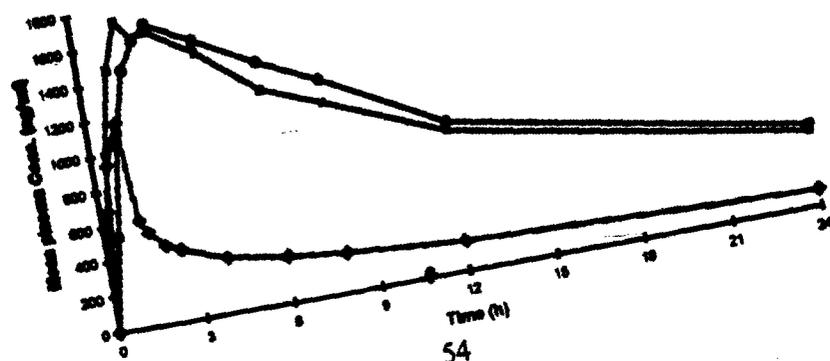
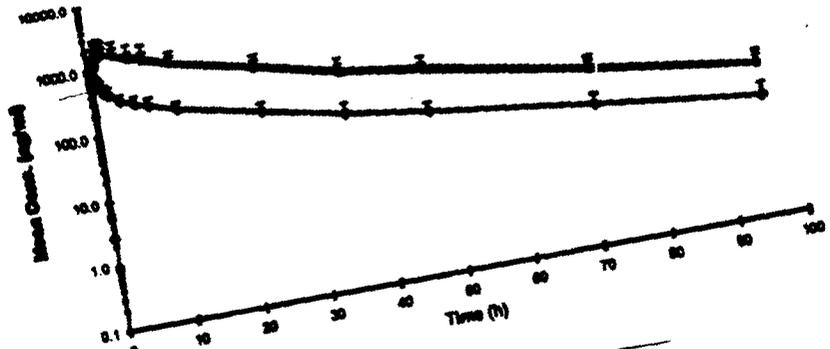


The assay is acceptable based on the current standard.

Pharmacokinetics:

Following a 400 mg oral dose, STI571 was completely absorbed and was almost completely bioavailable (>97%). The oral solution was bioequivalent with the capsule formulation of STI571 as assessed by comparing AUC, C_{max} and t_{max} of the parent compound.

Figure. Mean plasma concentration - time profile of STI571 following i.v. (100 mg) and p.o. (400 mg) administration; capsule (open circles), solution (open squares), i.v. (open diamonds)



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